# REMARKS

## I. THE AMENDMENTS TO THE CLAIMS

The present invention relates to a method of screening compounds to identify those with activity toward stabilizing p53, because, as explained in the application, such compounds have indications in the field of oncology.

### A. Basis for claims

Although a newly numbered set of claims has been presented for convenience and ease of reading, most of the new claims specify limitations that are similar or identical to limitations found in claims in the previous claim set, as shown by the following claim correspondence chart (citations to the specification are in parentheses):

| **Pending Claim** | *Previous Claim* | | **Pending Claim** | *Previous Claim* | | **Pending Claim** | *Previous Claim* |
|---|---|---|---|---|---|---|---|
| 56 | *56* | | 72 | *38* | | 88 | *35* |
| 57 | *26* | | 73 | *48* | | 89 | *34* |
| 58 | *26* | | 74 | *49* | | 90 | *33, 34* |
| 59 | *42* | | 75 | *50* | | 91 | *34* |
| 60 | *26* | | 76 | *52* | | 92 | *30* |
| 61 | *26* | | 77 | *53* | | 93 | *29* |
| 62 | *26* | | 78 | *51* | | 94 | *36* |
| 63 | *(pp.35-36)* | | 79 | *39* | | 95 | *31* |
| 64 | *(pp. 15, 35-36)* | | 80 | *40* | | 96 | *32* |
| 65 | *34, 43, 47* | | 81 | *41* | | 97 | *32* |
| 66 | *43* | | 82 | *27* | | 98 | *28* |
| 67 | *44* | | 83 | *37* | | 99 | *55* |
| 68 | *45* | | 84 | *34, 37* | | 100 | *26* |
| 69 | *46* | | 85 | *29, 37* | | 101 | *26* |
| 70 | *46* | | 86 | *29, 33* | | 102 | *34* |
| 71 | *47* | | 87 | *34* | | 103 | *34* |

In any case, all of the claims find support in the application as originally filed, e.g., at pp. 14-16 and 33-40, and the amendment does not introduce new matter. The Applicants do not intend by these amendments to abandon the subject matter of any claim previously presented, and reserve the right to pursue such subject matter in related applications.

**B. Patentability over the prior art of record.**

There were no prior art rejections in the outstanding Office action. Nonetheless, the following remarks may be helpful insofar as the Patent Office (in an action dated June 3, 2004) previously cited Welch US 5,900,360 as allegedly anticipatory prior art with respect to other claims. The prior art rejection does not apply to the new claims. Applicant also reiterates all remarks made in its paper of March 20, 2006 (see Page 7 thereof referring to Pages 15-16 of the Specification) including as to the definition of "specific interaction", i.e. directed to compounds that distinguish over bulk solvent effects, for example. It should be noted that lacking any knowledge of the "specific interactions" that are possible between effective drug molecules and proteins of the p53 family (as published by the present inventors in Science, and then adopted and copied by other pharmaceutical companies, see Applicant's prior remarks of record), there would have been no motivation , nor has there been conducted an assay to actually measure interaction between the compound and the p53 polypeptide.

In columns 8-9, Welch mentions both "physical property" assays and "biological activity" assays for proteins. However, with respect to p53, Welch only describes cell-based assays involving a cell line ("generous gift from A. Levine") expressing a temperature sensitive p53 mutant. The first assay involved elevating the temperature of the cells in the presence or absence of chaperone proteins, and then assaying to determine the *intracellular distribution* of p53. The allegedly stabilizing agents caused localization of the p53 into the nucleus, whereas control cells showed accumulation in the cytoplasm. Welch's second p53 assay involved the same cell line, and purported to assay the test agent's effects on p53 function, where a stabilizing agent should cause cell cycle arrest, whereas control cells allegedly continued to proliferate. (See Example 3.)

Among the features of this claim set that are neither disclosed nor suggested by Welch:

-- an assay involving isolated p53;

-- an assay requiring analysis of binding between a test agent and p53;

-- an assay involving analysis of p53 binding to DNA;

-- an assay using epitope specific antibodies to assay effects on p53 conformation;

-- use of a human p53;

-- use of a fragment of p53; and

-- an assay performed under physiological conditions.

With these introductory comments, the Applicants address the outstanding rejection in the case in the next section.

## II. THE REJECTION ALLEGING LACK OF ENABLEMENT SHOULD BE WITHDRAWN.

The only rejection in the case pertains to alleged lack of enablement. The Applicants agree that the CAFC's *In re Wands* opinion outlined relevant considerations for enablement, but disagree with the Examiner's analysis and rejection.

### A. The nature of the invention.

The Examiner asserts that the "invention is in the field of cancer treatment" and "is drawn to methods of stabilizing mutant forms of tumor suppressor proteins of the p53 family." (Action at p. 3.) These characterizations are incorrect, and they have skewed the entire analysis of enabling disclosure in this case.

The current invention pertains to drug discovery. Irrespective of whether "the field of cancer treatment" is complex, as alleged by the Examiner, the field of screening assays is less complex. Cancer therapy ultimately is successful when the growth of cancer is inhibited, for example. The claims are drawn to a method of screening compounds to identify compounds with a specified activity that may be useful for development as drugs. The success of a screening assay is measured by the ability to identify those compounds, among potentially many tested, that have a specific activity or property. In the current claims, the property being tested is, e.g., restoring or stabilizing a functional conformation of the polypeptide. However, the claims are

not drawn to methods of stabilizing p53 polypeptides *per se*. The claims are drawn to the screening assay.

**B. The state of the art and predictability**

The Examiner alleged, "The state of the art, pharmacology, involves screening *in vitro* and *in vivo* in order to determine which compounds exhibit pharmacological activities. There is no reasonable predictability even in view of the seemingly high level of skill in the art." It is unclear what the Examiner is requiring to be "predictable" in order to practice the invention. The invention as presently claimed is drawn to a screening method, with steps that entail, e.g., contacting agents together and measuring particular interactions. There is nothing unpredictable about the ability of the highly skilled person to perform the contacting step or make the measurement, or score a compound as one that stabilizes (or one that does not) based on the measurement taken. The state of the art of performing assays steps is predictable.

It appears that the Examiner is concerned about the predictability of *properties of compounds*. For example, the Examiner speaks of "the instantly claimed compounds or pharmaceutical compositions" in the Office action, at p. 4. The Applicants are not presently claiming compounds or compositions. Thus, the discussion of them is irrelevant because the screening assay does not require prior knowledge or prediction of the activity of compounds to be tested.

The Examiner also expresses concern about the capability of detecting "the disclosed minimal concentration of 1 mM or less." This statement appears to be irrelevant to the current claim set. Moreover, it is difficult to understand because scientists in the field routinely work with concentrations of biological or organic molecules that are orders of magnitude lower than millimolar, and medicines are routinely administered in amounts that achieve sub-millimolar concentrations *in vivo*. With respect to practicing the invention, labeled antibodies, for example, are routinely used in quantitative assays to measure the presence or absence of target epitopes at concentrations that are orders of magnitute lower than 1 mM. To provide another example, avidins/steptavidins have an affinity toward biotin ($K_d \approx 10^{-14}$–$10^{-16}$ M) that has allowed these molecules to be used to detect concentrations or compounds that are many orders of magnitude below 1mM. If the Examiner persists in this rejection, the Applicants request

clarification of what measurement *relevant to the claimed screening assay* is believed to be beyond the realm or ordinary skill.

As to how the "state of the prior art" influences the question of enablement, the correct answer is that it supports a conclusion of enablement. Although the invention should be considered a breakthrough and unobvious, the state of the art pertaining to how to practice screening methods generally, with steps that involve contacting molecules together and taking measurements, is quite mature. Companies in the field of drug development are equipped to perform such assays in a largely automated fashion, in high throughput formats.

**C. Amount of direction or guidance.**

The Examiner concludes (without analysis) that the amount of direction or guidance is "deficient." What is clear from the action, again, is that the analysis was wrongly focused, because the Examiner was looking for direction or guidance "in light of the nature of the alleged invention (treatments for cancer)." The "alleged invention" that is analyzed should be the invention that is claimed, e.g., a screening assay. Pages and pages of the application are directed to descriptions of how one performs steps of the screening assay. (See, e.g., Section C, pages 33-40; and Examples.)

As explained in the preceding section, the discussion of concentration in the action is confusing because those of skill in the art routinely work with reagents at concentrations in the millimolar or micromolar (or lower) range. However, the issue is largely moot with respect to the present claims, which are not limited in this manner. Claim 62 effectively requires performing an assay with 1 mM or less of a compound. It is within the skill of a high school chemistry student to perform a dilution of a compound to make a solution of 1 mM or less, for use in assays.

**D. Working examples**

The Examiner acknowledges the presence of working examples but expresses concern about "the embodiment of the invention of being able to elicit a therapeutic effective response by use of 1mM or less of said compound." This particular issue is moot with respect to

the current claims, which have no concentration limitation. The only claim that presently recites a concentration limitation – claim 62 – requires use of 1 mM or less concentration *in a binding assay*. Claim 62 does not specify a therapeutic response. *However*, it should also be noted that the application contains examples of compounds that were shown to be effective at sub-millimolar concentrations. (See, e.g., p. 44, Table 2). Thus, the consideration of working examples supports a conclusion of patentability.

The Examiner acknowledges that the application teaches an example of a compound with sub-millimolar activity but alleges that "applicant has failed to satisfy a duty to disclose evidence supporting such a conclusion." The Applicants respectfully submit that the patent statute does not specify such a duty, and the Patent Office has not asked for any specific data.

At pages 5-6 of the action, the Examiner discusses terms such as "native conformation," "functional conformation," "physiological conditions," and "stabilization." Although it is not entirely clear, the Examiner's concern appears to be whether or not the assay "sufficiently emulates" tumor cells. It is not entirely clear how these discussions are relevant to the question of *enabling disclosure*.

To the extent that the Examiner is alleging doubt as to the *utility* of the present assays for a real world drug discovery program, the Applicants request that the Examiner substantiate such an allegation with evidence or a declaration. In the Applicant's submission dated March 17, 2005, the Applicant presented evidence that the scientific community has considered this invention, published in the prestigious journal *Science*, to be important to the field; and also presented evidence that a competitor has used the invention to identify a drug candidate.

The issues raised by the Examiner also are not relevant to whether one of ordinary skill can practice the invention. The application describes binding and conformation assays at pages 35-39, for example. The Examiner's speculation about whether conformation is "native" or "functional" or how those words relate to each other does not detract from the fact that the application teaches how to perform the steps recited in the claims.

**E. "The art"**

The Examiner makes conclusory allegations about "variant factors" and "exhaustive experimentation" – again in the context of "the nature of the invention (treatment of cancer)." The Examiner continues to focus on whether there is sufficient evidence that a compound at a concentration of 1 mM or less could reasonably be an effective treatment for cancer in a method the involves steps of contacting and measuring. The claimed invention is not directed to treatment of cancer. The claimed method is a screening method, and it is enabled if a person of ordinary skill is able to perform the "contacting" and "measuring" steps and able then to draw the indicated conclusion about a test compound based on the measurements taken.

With respect to the *Wands* inquiry concerning "the art," it is clear that the art of screening is high and scientists in the field have developed excellent tools for automating high throughput assays to screen huge numbers of compounds. The art favors a conclusion of enablement in this case.

**F. Level of skill**

The Examiner acknowledged in the action the "seemingly high level of skill in the art." This factor also supports a finding of enablement.

**G. Conclusion**

From the foregoing discussion, it should be apparent that the invention that is currently being claimed pertains to a screening assay useful for identifying candidates for development of new drugs. There is a robust description of the materials to be used in the assays and of the methods for carrying them out. All of the *Wands* factors support a conclusion of enablement, and the rejection appears to have been based on an improper perception that the invention is directed to a method of treating cancer. For all of the reasons above, the rejection for lack of enabling disclosure should be withdrawn.

## III. CONCLUDING REMARKS

For the foregoing reasons, the Applicant requests withdrawal of the rejection for lack of enablement and allowance of the pending claims. The Examiner is invited to contact the undersigned attorney if the Examiner has questions or believes that a discussion of any issue could expedite allowance.

Respectfully submitted,

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